PharmaNote®
Vol. 35, Issue 5 February 2020 Established 1985

Rybelsus© (oral semaglutide); An Easy Pill to Swallow in a Class of Injectables

Rachel Perry, PharmD Candidate

Diabetes mellitus is a chronic metabolic condition categorized into two broad categories: type I and type II. Type I diabetes mellitus is characterized by an absolute deficiency of insulin whereas type II diabetes mellitus (T2DM) is caused by insulin resistance and beta cell dysfunction. Diabetes mellitus affects ~30 million Americans, with 1.5 million new diagnoses each year and represents the 7th leading cause of death in the United States.[1] T2DM accounts for nearly 95% of all diabetic cases and requires a multifactorial patient-centered approach when choosing pharmacologic therapy. It is also crucial to consider a patient's comorbidities and preference when developing a complete care plan for these patients.

The American Diabetes Association (ADA) continues to recommend metformin as the first-line initial treatment in T2DM in combination with lifestyle modifications. Many patients with T2DM however, will require combination therapy with metformin to achieve adequate glycemic control.[2] Management of T2DM should be guided based on glucose levels as well as other comorbidities that may be present such as obesity and cardiovascular risk factors (hypertension and hyperlipidemia).[2] For patients with comorbid atherosclerotic cardiovascular disease (ASCVD), heart failure, or chronic kidney disease, adding a glucagon-like peptide 1 receptor agonist (GLP-1 RA) or sodium glucose transporter inhibitor (SGLT2) is the recommended added pharmacological therapy to metformin based on their demonstrated cardiovascular risk reduction. Oral medications are often preferred by patients due to simplicity and convenience, however, many are not be able to achieve their target HbA1C with oral therapy and require injectable medications such as insulin or glucagon-like peptide 1 receptor agonists (GLP-1 RAs). Injectable medications can have a significant burden on patients and may lead to patient non-adherence due to needle aversion, high costs, and the side effect profile. If a patient with T2DM is not severely uncontrolled (A1C <10%, blood glucose <300 mg/dL, or no symptoms of hyperglycemia), the ADA suggests that adding a GLP-1 RA may be an appropriate addition to a patient's anti-hyperglycemic regimen due to their lower risk of hypoglycemia and beneficial effects of weight loss and cardiovascular risk reduction.[2] The development of an oral formulation of semaglutide has recently been FDA approved for the treatment of T2DM, offering patients and physicians another treatment option from the GLP-1 RA class of medications. This may help alleviate some of the patient barriers in receiving this life saving therapy. The purpose of this paper is to compare the effectiveness of oral semaglutide vs other available anti-hyperglycemic agents commonly used in managing patients with T2DM.

Clinical Pharmacology

In healthy individuals, GLP-1 is released after oral ingestion of carbohydrates or fats to help regulate glucose homeostasis in a glucose-dependent manner. Semaglutide is a GLP-1 analogue of human GLP-1, with 94% sequence homology that binds to and activates the GLP-1 receptor to maintain glucose homeostasis. This action enhances insulin secretion and beta-cell proliferation, suppressing glucagon secretion, delaying gastric emptying, and increases satiety.[3] Prior to the development of oral semaglutide, GLP-1 RAs were only available as injectable therapy. Protein and peptide-based drugs when administered orally have a limited bioavailability due to proteolytic enzymes and acidic environment of the stomach as well as having decreased permeability through the gastric epithelium.[4] Oral semaglutide is co-formulated with salcaprozate sodium or SNAC (sodium N-(8-[2-hydroxybenzoyl] amino) caprylate) to facilitate the absorption of semaglutide after oral administration leading to increased systemic bioavailability.[5] Systemic exposure increases in a dose-proportional manner reaching steady state concentrations of 6.7 nmol/L and 14.6 nmol/L with respective 7 mg and 14 mg oral semaglutide after 4-5 weeks of once daily dosing.[6] The peak plasma concentration is achieved one hour post-dose and has a bioavailability of 0.4%- 1%.6 Semaglutide has a volume of distribution of 8 L and is highly protein bound, which contributes to its extended half-life of ~one week. Oral semaglutide is metabolized primarily by proteolytic cleavage of the peptide backbone and subsequent beta-oxidation of the fatty acid side chain and is excreted via urine and stool.[6] A summary of the pharmacokinetics is listed in **Table 1.**

In This Issue

Clinical Trials

The following section will review two phase II and several phase III trials of oral semaglutide from the PIONEER clinical trial series. The PIONEER trial series evaluated the efficacy of oral semaglutide compared to placebo as well as other commonly prescribed anti-hyperglycemic classes of medications. The results of these trials are summarized in **Table 2** and **Table 3**.

Phase II

Granhall et al conducted two randomized, placebo-controlled, double blind trials to determine the safety and pharmacokinetics of oral semaglutide with different doses of SNAC. The first of these two trials studied only a single dose of oral semaglutide with the second study looking at multiple ascending doses.[5] Subjects in both studies were excluded if they had clinically significant concomitant diseases or disorders, clinically significant abnormal values in laboratory screening tests, any history of GI surgery (except uncomplicated procedures), or if they smoked more than five cigarettes per day.

Single-Dose

The single-dose trial tested various strengths of oral semaglutide co-formulated with different amounts of SNAC to determine the safety and pharmacokinetics profile of oral semaglutide. This trial enrolled 135 subjects to receive the trial product or placebo with matching amounts of SNAC and consisted of 3 parts; a sequential dose escalation and two parts that tested doses in a parallel design. The doses tested were 2 mg semaglutide with 300 mg SNAC (n=24) vs placebo with SNAC (n=2), 5 mg semaglutide with 300 mg SNAC (n=24) vs placebo with SNAC (n=2), 10 mg with 300 mg SNAC (n=24) vs placebo with SNAC (n=2), and 20 mg semaglutide with 600 mg SNAC (n=10) vs placebo with SNAC (n=2). A safety group decided if a subject could proceed to the next dose level. The doses in the next part tested 5 mg semaglutide with 150 mg SNAC, 10 mg semaglutide with 600 mg SNAC, and 15 mg semaglutide with 450 mg SNAC. The last part of the trial tested 3 doses from the first part of the trial and, 2 mg semaglutide with 300 mg SNAC, 5 mg semaglutide with 300 mg SNAC, and 10 mg semaglutide with 300 mg SNAC in a parallel fashion. Subjects were instructed to come to clinic after fasting for at least ten hours before dosing, received one dose with 50 mL of water, and then fasted for five hours post-dose. Subjects were monitored at the clinic for eight days after dosing.

Subjects included healthy males aged 18–50 years with a bodyweight of 65.0–95.0 kg and a body mass index (BMI) of 18.5 –27.5 kg/m2. The primary endpoint evaluated safety assessments including adverse events (ADE), hypoglycemic episodes, laboratory safety parameters, vital signs, and an electrocardiogram. The researchers compiled all the subjects receiving placebo with SNAC into one group when evaluating adverse events. A total of 104 ADE reported in 55 patients across all treatment groups, including placebo with SNAC. The most commonly reported ADE patients reported were headaches 15% vs 4% and gastrointestinal events 14% vs 13% in the oral semaglutide vs placebo groups, respectively. Specific ADEs were not reported with the trial. The majority of ADEs with the single-dose trial were classified as mild in severity, with five being classified as moderate. All subjects recovered from their ADEs and none were withdrawn from the study. There were 13 confirmed hypoglycemic episodes in 9 subjects, but none were determined to be severe, requiring 3rd party assistance and confirmatory plasma glucose < 3.1 mmol/L (~55.9 mg/dL). No changes in vital signs, laboratory safety parameters, physical examinations, or ECGs were reported as clinically relevant. The semaglutide plasma concentrations were thought to be underestimated due to a matrix effect with the assay that was used (luminescence oxygen channeling immunoassay) resulting in fewer subjects (48/112) with measurable semaglutide plasma concentrations. The oral semaglutide plasma concentration was highest when co-formulated with 300 mg SNAC, compared to 150 mg or 600 mg SNAC, which suggested that this was the optimal amount to enhance absorption of oral semaglutide. The single-dose trial also showed that plasma concentrations of oral semaglutide increased as the dose of semaglutide increased due to a greater proportion of patients on higher doses achieving measurable semaglutide plasma concentrations. However, these results were not reported in the article.

Table 1 | Select Semaglutide Pharmacokinetics[6]

Absorption	
Cmax[a]	≤ 1 hour
Bioavailability	0.4%-1.0%
Distribution	
Vd[b]	8 L
Metabolism	
Proteolytic cleavage of peptide backbone —> beta-oxidation of fatty acid side chain	
Elimination	
T1/2[c]	~7 days

[a]Maxmium concentration; [b]Volume of distribution; [c]Half-life

Multiple-Dose

The multiple-dose trial enrolled 107 subjects, which tested semaglutide in a semi-parallel fashion in healthy males and males diagnosed with T2DM. This trial included 84 healthy males aged 18-64 years old with a BMI of 20.0–29.9 kg/m2 and 107 males aged 18-64 years old with T2DM that were diagnosed within the past 10 years and treated with diet and exercise, with or without metformin, had a BMI of 20.0–37.0 kg/m2, and had an HbA1C of 6.5%-9.0%. This trial was originally intended to study the safety of once-daily oral semaglutide for ten weeks with maintenance doses of 20 mg, 40 mg, and 60 mg in healthy subjects vs placebo and placebo with SNAC and 60 mg semaglutide in subjects with T2DM vs placebo and placebo with SNAC. Dosing was achieved in a stepwise manner, starting with 5 mg for the first week and then doubling the dose thereafter weekly. Subjects were to only be escalated to 40 mg and 60 mg if determined appropriate by the safety group; however, the safety group determined that after subjects reached 40 mg dose of semaglutide, 60 mg semaglutide would result in too many ADEs. Therefore, subjects randomized to receive semaglutide 60 mg were combined into the semaglutide 40 mg cohort. This trial utilized plasma protein precipitation and liquid chromatography with a lower limit of quantification as an assay to evaluate the semaglutide concentration-time profile. to determine bioavailability.

The primary endpoint of the multiple-dose trial was the number of adverse events. Gastrointestinal disorders were the most commonly reported adverse effects with 50% (n=8/16), 84% (n=27/32), 28% (n=5/18), and 72% (n=13/18) of healthy subjects reporting events in the semaglutide 20 mg, semaglutide

Table 2 | Primary Endpoints from PIONEER Series Trials[7-9]

Trial	Intervention	Primary Endpoint	Results		
PIONEER 2[7]	Semaglutide 14 mg PO[a] daily Empagliflozin 25 mg PO daily	Change from baseline HbA1C[b] at week 26	-1.3% vs –0.9%	ETD[c] –0.4% (95% CI[d] –0.6 to -0.3)	p[e]<0.0001
PIONEER 3[8]	Semaglutide (3, 7, or 14 mg) PO daily Sitagliptin 100 mg PO daily	Change from baseline HbA1C at week 26	3mg/d: -0.6% vs –0.8% 7 mg/d: -1.0% vs –0.8% 14 mg/d: -1.3% vs –0.8%	ETD 0.2% (95% CI 0.0% to 0.3%) ETD –0.3% (95% CI –0.4% to –0.1%) ETD –0.5% (95% CI –0.6% to –0.4%)	p<0.008 p<0.001 p< 0.001
PINOEER 4[9]	Semaglutide 14 mg PO daily	Change from baseline HbA1C at week 26 (semaglutide vs liraglutide)	-1.2% vs –1.1%	ETD –0.1% (95% CI –.03% to 0.0%)	p<0.0001**
	Liraglutide 1.8 SQ daily Placebo	Change from baseline HbA1C at week 26 (semaglutide vs placebo)	-1.2% vs –0.2%	ETD –1.1% (95% CI –1.2% to –0.9%)	p<0.0001

[a]By mouth; [b]Glycosylated hemoglobin; [c]Estimated treatment difference; [d]Confidence interval; [e]P-value
**p-value for non-inferiority

40 mg, placebo, and placebo with SNAC treatment groups, respectively. In subjects with T2DM, 73% (n=8/11), 50% (n=3/6), and 33% (n=2/6) of subjects reported gastrointestinal disorders for 40 mg oral semaglutide, placebo, and placebo with SNAC respective treatment groups. The severity of reported adverse events increased as the dosing of semaglutide was increased with 0% (n=0/16), 28% (n=9/32), 16% (n=3/18), and 0% (n=0/18) subjects experiencing severe adverse events in the 20 mg semaglutide, 40 mg semaglutide, placebo, and placebo with SNAC treatment groups, respectively. Adverse events in the T2DM cohort occurred in 9% (n=1/11), 16% (n=1/6), and 0% (n=0/6) in the 40 mg semaglutide, placebo, and placebo with SNAC treatment groups, respectively. There were four serious adverse events reported in three subjects, which were vomiting, atrial fibrillation, upper abdominal pain, and aortic aneurysm. All subjects recovered from the adverse events. A total of 15 subjects withdrew from the trial due to adverse events of decreased appetite and nausea, vomiting, increased lipase, aortic aneurysm, atrial fibrillation, or medication error. Four hypoglycemic events occurred in healthy patients, but none were determined to be severe. The 40 mg semaglutide resulted in maximum plasma concentrations and area under the curve that were about twice that of the 20 mg semaglutide group. The half-life was comparable among treatment groups at approximately one week.

The T2DM treatment group had a statistically significant reduction in HbA1C -1.5% from baseline (7.5%) (95% CI -1.8 to -1.3, p< 0.001) vs placebo and placebo with SNAC. Both healthy subjects and subjects with T2DM subjects showed statistically significant reduction in bodyweight after 10 weeks of treatment with oral semaglutide with -4.3 kg for 20 mg (95% CI -6.3 to -2.3, p<0.001) and -7.2 kg for 40 mg (95% CI -8.9 to -5.4) in healthy subjects and -5.4 kg (95% CI -8.5 to -2.3, p<0.001) in T2DM subjects. There was no systematic decrease in mean systolic blood pressure in healthy subjects, however, T2DM subjects receiving the 40 mg oral semaglutide dose achieved a 13 mmHg decrease from 142 mmHg baseline compared to placebo.

Phase III (PIONEER Series)

PIONEER 2

PIONEER 2 is a phase III clinical trial that compared the efficacy of oral semaglutide to empagliflozin in T2DM patients uncontrolled on metformin.[7] This trial was conducted at 108 sites in 12 countries. Patients were included if they were at least 18 years of age, had a diagnosis of T2DM at least 90 days before screening, had an HbA1C of 7.0-10.5%, and on a stable dose of at least 1500 mg or maximum tolerated dose of metformin at least 90 days before screening. Patients were excluded if they had used any medication for diabetes or obesity other than metformin or short-term insulin (≤14 days) in the 90 days prior to screening, renal impairment with eGFR<60 mL/min, had proliferative retinopathy or maculopathy requiring acute treatment, were female and pregnant or breastfeeding, had a disorder that may risk their safety or compliance to the protocol, family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma, a history of pancreatitis, GI surgeries that could impact the absorption of the medications, a history of MI, stroke, or unstable angina or TIA in the previous 180 to screening, history of New York Heart Association (NYHA) Class IV heart failure, and history of DKA. Efficacy was determined by using treatment policy and trial product estimands including those who discontinued the trial product or used rescue medication, which reflects the intention-to-treat principle. The trial product estimand reflects the effect for all patients that continued the trial product for the duration of the trial without using rescue medication and will be the result values reported, although results were similar between the two estimands.

The primary endpoint, which tested for superiority and non-inferiority, was the change in HbA1C from baseline at the end of the 26 week trial. Secondary endpoints included change in HbA1C from baseline to week 52 as well as changes from baseline to weeks 26 and 52 in body weight fasting blood glucose (FBG), self-measured blood glucose, fasting c-peptide, fasting insulin and glucagon, BMI, waist circumference, and fasting lipid profile. The trial enrolled 822 patients who were randomized to oral semaglutide 14 mg once daily (n=412) or empagliflozin 25 mg once daily (n=410). Baseline characteristics were similar between treatment groups in terms of sex, mean age (58 years), baseline HbA1C 8.1%, FBG 173 mg/dL, average duration of diabetes of 7.4 years, and mean body weight of 91.6 kg. Additional anti-hyperglycemic medication was used in 17 patients (4.1%) and rescue medication was used in 8 (1.9%) of patients.

The 14 mg oral semaglutide group proved to be superior compared to empagliflozin 25 mg in the primary endpoint of re-

Table 3 | Select Secondary Endpoints from PIONEER Series Trials[7-9]

Trial	InterventionS	Primary Endpoint	Results		
PIONEER 2[7]	Semaglutide 14 mg PO[a] daily	Change from baseline body weight (kg) at week 26	-3.8 vs –3.7	ETD[c] –0.1 (95%CI[d] –0.7 to 0.5)	P[e]= 0.7593
	Empagliflozin 25 mg PO daily	Change from baseline FPG[B] (mg/dL) at week 26	-35.9 vs –36.3	ETD 0.4 (95%CI –4.3 to 5.0)	p= 0.8812
PIONEER 3[8]	Semaglutide (3, 7, or 14 mg) PO daily	Change from baseline body weight (kg) at week 26	3mg/d: -1.2 vs –0.6	ETD –0.6 (95% CI –1.1 to –0.1)	p=0.02
			7 mg/d: -2.2 vs –0.6	ETD –1.6 (95% CI –2.0 to –1.1)	p<0.001
			14 mg/d: -3.1 vs –0.6	ETD –2.5 (95% CI –.0 to –2.0)	p< 0.001
	Sitagliptin 100 mg PO daily	Change from baseline FPG (mg/dL) at week 26	3mg/d: -13.6 vs –13.9	ETD 1.9 (95% CI –3.6 to 7.3)	p=0.50
			7 mg/d: -21.3 vs –13.9	ETD –5.9 (95% CI –11.4 to –0.3)	p=0.04
			14 mg/d: -30.5 vs 13.9	ETD –15.1 (95% CI –20.6 to –9.7)	p<0.001
PINOEER 4[9]	Semaglutide 14 mg PO daily	Change from baseline body weight (kg) at week 26	-4.4 vs –3.1	ETD –1.2 (95% CI –1.9 to -0.6)	P=0.0003
	Liraglutide 1.8 SQ daily	Change from baseline FPG (mg/dL) at week 26	-36 vs –33.7	ETD –0.13 (95% CI –0.41 to –0.14)	P=0.0136

[a]By mouth; [b]Fasting plasma glucose (mg/dL); [c]Estimated treatment difference; [d]Confidence interval; [e]P-value

duction in HbA1C -1.3% vs -0.9% (95% CI -0.6 to -0.3, p <0.0001) at week 26. There was no significant difference between treatment groups in FBG. Both semaglutide and empagliflozin groups had similar reductions in FBG at weeks 26 and 52 and had similar weight loss at week 26, -3.8 vs -3.7 kg (95% CI -0.7 to 0.5, P= 0.7593), however, the semaglutide showed statistically significant weight reductions at 52 weeks of -4.7 kg compared to -3.8 kg in the empagliflozin treatment group (95% CI -1.6 to -0.2, p= 0.0114) at week 52. The self-measured blood glucose did show statistically significant reductions at week 26 baseline, but little change from week 26 to 52; -0.3 (95% CI -0.5 to 0.0) vs -5.0 (95% CI -9.5 to 0.6) with p=0.0267 and week 26 and -0.3 (95% CI -0.5 to -0.0) vs -5.1 (95% CI -9.7 to -0.4) with P=0.328.

The most commonly reported adverse event in this study was nausea and was typically determined to be mild to moderate severity. Fewer serious adverse events were reported in the oral semaglutide treatment group (6.6% vs 9.0%) however, premature discontinuation of the trial product due to adverse events was more frequent in the oral semaglutide group (10.7% vs 4.4%) and were primarily related to GI symptoms, with nausea being the most frequently reported adverse event (19.8% vs 2.4%).

PIONEER 3

The PIONEER 3 trial is a 78 week phase 3 clinical trial evaluating the safety and efficacy of oral semaglutide vs sitagliptin as adjunct therapy in T2DM patients uncontrolled on metformin with or without a sulfonylurea.[8] The trial was conducted at 206 sites, including 14 countries, from February 2016 to March 2018. Patients were included in this study if they had a diagnosis of T2DM with an HbA1C of 7.0%-10.5% and were taking a stable dose of metformin with or without a sulfonylurea. Patients were excluded if they received diabetes treatment other than metformin, sulfonylurea, or short-term insulin (≤14 days), treatment for obesity in the previous 90 days before screening, had a history of pancreatitis, renal impairment, or proliferative retinopathy or maculopathy requiring treatment.

The primary endpoint of this study was a change in HbA1C and the key secondary endpoint was change in body weight from baseline to week 26. These outcomes were also assessed at weeks 52 and 78 as additional secondary endpoints. Researchers tested outcomes for non-inferiority and superiority. The trial enrolled 1664 subjects, which were randomized to receive 3 mg (n=466), 7 mg (n=466), or 14 mg (n=465) of once-daily oral semaglutide or once-daily 100 mg sitagliptin (n=467). Subjects were instructed to take trial product in the morning, fasted with a glass of 120 mL of water at least 30 minutes before breakfast or taking any other medications. Patients continued their background metformin with or without sulfonylurea through the remainder of the trial.

For the primary outcome at week 26, oral semaglutide 3, 7, 14 mg/day, showed a mean decrease in HbA1C from baseline of 0.6%, 1.0%, and 1.3% respectively, compared a reduction of 0.8% for sitagliptin 100 mg. Semaglutide 7 mg and 14 mg groups were superior to sitagliptin in reducing HbA1C with differences from sitagliptin HbA1C reductions of -0.3% (95% CI -0.4% to -0.1%, P<.001) and -0.5% (-0.6% to -0.4%, P<.001), respectively. The 3 mg dose of oral semaglutide resulted in a smaller reduction of HbA1C, however, non-inferiority was not established as the differences in A1C lowering were not statistically significant. At week 26, the mean changes in bodyweight for semaglutide 3, 7, and 14 mg/d were -1.2 kg, -2.2 kg, and -3.1 kg respectively and -0.6 kg for sitagliptin. The 7 and 14 mg/d dosages were shown to have statistically significant superiority in HbA1C reduction when compared to sitagliptin with treatment difference of -1.6 kg (95% CI -2 to -1.1, p<0.001) and -2.5 kg (95% CI -3 to -2, p<0.001), respectively. Superiority was not evaluated for the 3 mg/d dose of semaglutide due to the inability for the researchers to demonstrate non-inferiority in regard to HbA1C. There was no statistical significance for reduction in 7-point self-measured whole-blood glucose at weeks 26, 52, and 78 for semaglutide 7 mg and 14 mg vs sitagliptin 100mg. Additional secondary endpoints of HbA1C < 7.0% and weight reduction of ≥5% showed statistical significance in the 7 mg and 14 mg doses of oral semaglutide at weeks 26, 52, and 78 in comparison to sitagliptin. Additionally, the 3 mg oral semaglutide treatment group achieved a statistically significant reduction in weight from baseline at week 78, but not at weeks 26 or 52.

The proportion of patients that experienced an ADE leading

to early discontinuation of the study drug were 5.6% (26/466), 5.8% (27/464), and 11.6% (54/465) in the respective 3 mg, 7 mg, and 14 mg oral semaglutide treatment groups and 5.2% (24/466) for the sitagliptin treatment group. The authors suggest that the rate of discontinuation in the 14 mg oral semaglutide were comparable to other premature discontinuation rates with subcutaneous semaglutide and other trials with GLP-1 RAs. Gastrointestinal ADE were the primary cause of premature discontinuation across all treatment groups. The researchers reported that symptomatic hypoglycemic events mainly occurred in patients taking background medications metformin and a sulfonylurea and were experienced by 4.9% (23/466), 5.2% (24/464), 7.7% (36/465) in the respective 3 mg, 7 mg, and 14 mg oral semaglutide treatment groups and 8.4% (39/466) for the sitagliptin treatment group. Deaths occurred in five, three, and one patients in the 3 mg, 7 mg, and 14 mg semaglutide treatment groups and three patients in the sitagliptin group with no pattern of causes of death across treatment groups.

PIONEER 4

PIONEER 4 was a 52-week trial that compared the efficacy of oral semaglutide to another in-class GLP-1 RA, subcutaneous liraglutide in patients with T2DM uncontrolled on metformin monotherapy.[9] The trial was conducted at 100 trial sites in 12 countries. Patients were eligible if they were at least 18 years old with a diagnosis of T2DM with an HbA1C 7-9.5%, on a stable dose of metformin (≥1500 mg or maximum tolerated dose) with or without an SGLT2 inhibitor. Patients were excluded if they were taking any medication other than metformin, SGLT2 inhibitor, or short-term insulin (≤14 days) for diabetes or obesity in the previous 90 days to screening, renal impairment (eGFR<60 mL/min), proliferative retinopathy or maculopathy requiring acute treatment, and history of pancreatitis. Patient baseline characteristics were similar across treatment groups in terms of gender, race, HbA1C, body weight, BMI, waist circumference, estimated glomerular filtration rate, and the number of patients on background SGLT2 inhibitor.

Patients were randomly assigned to oral semaglutide, subcutaneous liraglutide, or placebo once daily in addition to existing anti-hyperglycemic medication(s). Patients in the oral semaglutide group were initiated on a 3 mg daily dose and titrated up to 7 mg daily at 4 weeks and 14 mg at 8 weeks and continued this dose for the remainder of the trial. Those in the subcutaneous liraglutide group were initiated on a 0.6 mg once daily dose with an escalation to 1.2 mg after 1 week and then 1.8 mg maintenance dose after 2 weeks. Patients were prescribed rescue medication as additional glucose-lowering medication if blood glucose levels reached >240 mg/dL during weeks 8-13, >200 mg/dL from week 14 to the conclusion of the trial.

The primary endpoint was a change in HbA1C from baseline at week 26. The main secondary endpoint was a change in bodyweight from baseline to week 26. Additional secondary endpoints included change in HbA1C at week 52, change in bodyweight at week 52, change in fasting plasma glucose from baseline to weeks 26 and 52, self-measured blood glucose concentration, and fasting lipids from baseline to weeks 26 and 52. Safety endpoints were determined by the number of adverse events requiring treatment during exposure of the study drug up to 52 weeks. Oral semaglutide showed to be non-inferior in comparison to liraglutide with respective decreases in HbA1C of -1.2% and -1.1% (95% CI -0.3 to 0.0, p< 0.0001 for non-inferiority) and superior to placebo with respectivea decreases in HbA1C pf -1.2% and -0.2%, which was a statistically significant reduction in HbA1C at week 26 from baseline (95% CI -1.1% to -0.2%). Oral semaglutide resulted in superior reduction in body weight compared to liraglutide (-4.4 kg vs -3.1 kg, 95% CI -1.9 to -0.6, p= 0.0003) and placebo (-0.5 kg, 95% CI -4.7 to -3.0, p< 0.0001). Oral semaglutide resulted in more frequent adverse events in comparison to subcutaneous liraglutide, but the reported events were comparable with the GLP-1 RA class.

Special Populations

Chronic Kidney Disease

PIONEER 5 was a study to evaluate the efficacy and safety of oral semaglutide in T2DM patients with moderate renal impairment (estimated glomerular filtration rate of 30-59 mL/min per 1.73 m2) uncontrolled on metformin monotherapy.[10] Oral semaglutide showed a statistically significant reduction in HbA1C (-1% vs -0.2%) at week 26 from baseline (95% CI -1.0 to -0.6, p<0.0001) as well as reduction in bodyweight (-3.4 kg vs -0.9 kg; 95% CI -3.2 to -1.8, p<0.0001). The renal safety profile was consistent with other medications in the class of GLP-1 RAs.

Cardiovascular Disease

PIONEER 6 evaluated cardiovascular outcomes of oral semaglutide in patients with T2DM.[11] The studied patient populations were patients 50 years or older with cardiovascular risk or chronic kidney disease and patients older than 60 years with cardiovascular risk factors only. The primary outcome of this study was a first occurrence of a major cardiovascular event, which occurred in 61 of 1591 patients (3.8%) treated with oral semaglutide and 76 of 1592 patients (4.8%) in the placebo group (hazard ratio 0.79, 95% CI 0.57 to 1.11, p<0.001) showing non-inferiority for oral semaglutide compared to placebo. The researchers attributed the inability to show superiority in preventing cardiovascular outcomes with oral semaglutide in comparison to other trials with GLP-1 RA therapy to a smaller study size, background medications between treatment groups (more patients receiving placebo were also on SGLT2- inhibitor, which has proven cardiovascular benefits), and a shorter study duration.

Pregnancy and Lactation

Available data is insufficient to evaluate the safety of oral semaglutide in pregnant or breastfeeding patients.6 The risks and benefits of the mother and developing fetus or baby should be evaluated and only use if the benefits outweigh the risks. SNAC is excreted into breastmilk and may lead to an accumulation of SNAC levels in neonates as they have a decreased activity of UGT2B7, which is responsible for SNAC clearance.[6] According to the oral semaglutide package insert, breastfeeding is not recommended in patients that are being treated with oral semaglutide. Females planning to become pregnant should discontinue oral semaglutide at least 2 months before a planned pregnancy to allow for an adequate washout period.[6] Oral semaglutide has not been studied in pediatric populations.

Adverse Events

Gastrointestinal events were the most common cause for trial participants to discontinue treatment with oral semaglutide. Common GI adverse reactions, which occurred in ≥5% of people in clinical trials were nausea, abdominal pain, diarrhea, decreased

appetite, vomiting, and constipation.6 Infrequent GI adverse events occurred in <5% and included abdominal distension, dyspepsia, eructation, flatulence, gastroesophageal reflux disease, and gastritis. Hypoglycemic episodes were most commonly reported in patients that were taking metformin in addition to another anti-hyperglycemic agent. A list of common and infrequent ADEs reported with semaglutide can be found in **Table 4**.

Contraindications/Warnings

Oral semaglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with multiple endocrine neoplasia syndrome type 2 as well as in patients with a known hypersensitivity to semaglutide or any of its components.[6] Semaglutide-induced thyroid C-cell tumors were reported in mice and rats; this risk in humans has yet to be determined. Pancreatitis was a serious adverse event reported in clinical trials.[6] Patients should be monitored for signs and symptoms of pancreatitis such as severe abdominal pain that may or may not be accompanied by vomiting.[6] Patients with a history of diabetic retinopathy should be monitored for worsening of symptoms as rapid improvement in glucose management can cause a temporary worsening diabetic retinopathy. The concomitant use of oral semaglutide with an insulin secretagogue or insulin increases the risk of hypoglycemia.[6] Kidney function should be monitored when initiating or escalating semaglutide therapy as there have been post-marketing reports of acute kidney injury or worsening chronic kidney disease.[6]

Cost

Rybelsus© (ral semaglutide) will be competitively priced within the class of GLP-1 receptor agonists. The average wholesale acquisition cost for oral semaglutide is $772.43 annually, which is equivalent to Ozempic©(injectable semaglutide) and comparable to Victoza© (liraglutide) at $614.52 annually.[12] Currently, Rybelsus© is not covered by Medicare plans. Novo Nordisk claims to be working with health insurance providers for coverage as well as providing a savings card program for eligible patients costing patients as little as $10 per month.

Clinical Implications

Many patients with T2DM will require dual combination therapy to achieve their target HbA1C. GLP-1 RAs, including oral semaglutide, have consistently been shown to have superior HbA1C lowering effects, constituting better outcomes. These medications also cause a reduction in body weight, which provides clinical relevance as this can lead to decreased cardiovascular risk and improved quality of life. It is not known however, if patients experiencing nausea contributed to the reduction in body weight. The American Diabetes Association Standards of Medical Care in Diabetes stress the importance of the role GLP-1 RA therapy has in patients with T2DM, but utilization is low. Oral formulation of semaglutide could lead to earlier initiation of GLP-1 RA therapy as it provides patients a simpler and more convenient anti-hyperglycemic regimen in comparison to in-class injectable GLP-1 RAs, which may improve compliance. The oral semaglutide would have more frequent dosing compared to SC semaglutide (once daily vs weekly), but is comparable to other daily GLP-1 RA's.

Table 4 | Common Adverse Reactions of Oral Semglutide[3]

Common (>10%)	Incidence
Abdominal Pain	5.7-11%
Diarrhea	8.5-10%
Nausea	11-20%
Infrequent (1-10%)	**Incidence**
Cholelithiasis	0.4-1.5%
Constipation	3.1-6%
Dyspepsia	06-2.7%
Gastritis	0.4-2%
Hypoglycemia	1-6%
Retinopathy	3-4.2%
Vomiting	5-9.2%

A limitation of the phase II trial that evaluated the safety and pharmacokinetics of oral semaglutide was the assay used to measure plasma concentrations of semaglutide after a single dose, an arbitrary scale was used to present the semaglutide concentration-time profiles. Plasma concentrations were likely low due to semaglutide's limited bioavailability and the fact that it was only a single dose. However, pharmacokinetics were able to be more adequately measured in the multiple-dose trial most likely due to the accumulation of semaglutide exposure with its long half-life.[5]

In the PIONEER 3 trial, oral semaglutide was compared to a DPP-4 inhibitor, sitagliptin.[7] GLP-1 RAs and DPP-4 inhibitors are both incretin-based therapies commonly used in the treatment of T2DM that work to maintain glucose homeostasis without increasing risk of hypoglycemia when used as a monotherapy. DPP-4 inhibitors typically have a more modest decrease in HbA1C and a neutral effect on weight in comparison to GLP-1 RAs. However, DPP-4 inhibitors are not known to cause nausea and are generally well-tolerated whereas nausea is commonly reported with GLP-1 RAs. Choosing between a GLP-1 RA or DPP -4 inhibitor as adjunct therapy to metformin will be an important clinical decision as both of these agents will now be available as oral formulations and provide similar mechanisms of action.
In the PIONEER 3 trial, the 3 mg dose showed a 0.6% decrease in HbA1C from baseline, which is comparable to other antidiabetic agents with moderate HbA1C lowering effect (DPP4 inhibitors, SGLT2 inhibitors, and meglitinides), allowing clinicians the option to increase the dose with oral semaglutide if a greater reduction in HbA1C is needed.

The PIONEER 4 trial used an in-class active comparator with subcutaneous liraglutide. This was a fair comparator as the safety and efficacy data are clinically relevant when choosing to add on oral vs injectable GLP-1 RA therapy.[8] The PIONEER 6 trial was comparing oral semaglutide to placebo to evaluate cardiovascular outcomes, however this study allowed patients to participate if they were on background anti-hyperglycemic agents such as SGLT-2 inhibitors or sulfonylureas. These profiles mimic real-life clinical practice as patients are typically on multiple oral antidiabetic agents before initiating to injectable therapy, but these background medications could have skewed the results as more patients receiving placebo were also receiving an SGLT-2 inhibitor, which has proven cardiovascular benefit. The researchers also

concluded that because PIONEER 6 had similar hazard ratios to that of other GLP-1 RA trials in T2DM patients with cardiovascular disease, that they also provided the same benefit without preventing a significantly greater number of primary cardiovascular events. The PIONEER 5 and 6 trials were too short in duration in order to determine the true risk and benefit in patients with chronic kidney disease and/or cardiovascular disease.[10,11]

Strengths of the PIONEER trials included large sample sizes, similar sample size among treatment groups, similar in baseline characteristics in terms of ethnic background, sex, age, BMI, background diabetes medications, baseline HbA1C, and estimated glomerular filtration rate. Some limitations of the PIONEER trials included some variances among treatment groups in terms of comorbid conditions, including different baseline fasting blood glucose levels, which could show more significant results.

The results of these studies are clinically relevant due to the significant reduction in HbA1C and body weight with oral semaglutide allowing for better glucose control and reduction of cardiovascular risk factors resultant of weight loss. As many patients prefer oral agents to injectables, oral semaglutide provides patients another class of oral medication for managing their T2DM. Further studies with longer follow-up time are needed to determine the risks and benefits in patients with cardiovascular disease and/or chronic kidney disease. GLP-1 RAs are a second-line option for T2DM treatment in the current guidelines for patients that have cardiovascular disease. Clinicians and patients typically prefer to delay starting injectables as this can be a burden to the patient. If oral semaglutide can demonstrate cardiovascular benefit, clinicians may be more likely to initiate it earlier in a patient's antidiabetic regimen.

Conclusion

Rybelsus© (semaglutide) is the first oral medication in the GLP-1 RA class that has been fore the treatment of T2DM. The PIONEER trials series have shown this medication to significantly reduce HbA1C and bodyweight in comparison to some other commonly used anti-hyperglycemic agents, including other GLP-1 RA therapies. The most common side effect with this medication is nausea otherwise the medication appears to be well tolerated. Oral semaglutide has been shown to be safe and effective as an add-on therapy in patients with T2DM uncontrolled on metformin monotherapy and lifestyle changes.

Conclusion

1. Statistics about Diabetes. American Diabetes Association. Accessed November 7, 2019.
2. American Diabetes Association Standards of Medical Care in Diabetes—2019, 9: pharmacologic approaches to glycemic treatment. Diabetes Care. 2019. Accessed November 7, 2019.
3. Semaglutide. ClinicalPharmacology. 2019 Elsevier. Accessed November 7, 2019.
4. Buckley ST, Bækdal TA, Vegge A, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. Sci Transl Med. 2018.
5. Granhall, C., Donsmark, M., Blicher, T.M. et al. Safety and Pharmacokinetics of Single and Multiple Ascending Doses of the Novel Oral Human GLP-1 Analogue, Oral Semaglutide, in Healthy Subjects and Subjects with Type 2 Diabetes. Clin Pharmacokinetics. (2019) 58: 781-791.
6. Rybelsus [package insert]. Plainsboro, NJ. Novo Nordisk Inc. 2019
7. Helena W. Rodbard, Julio Rosenstock, Luis H. Canani, et al. Oral Semaglutide Versus Empagliflozin in Patients With Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial. Diabetes Care. 2019; 42 (11).
8. Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea: The PIONEER 3 Randomized Clinical Trial. JAMA. 2019;321(15):1466–1480. doi:10.1001/jama.2019.2942
9. Pratley R, Amod A, Hoff ST et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. The Lancet. 2019; 394 (10192): P39-50.
10. Mosenzon O, Blicher T, Rosenlund S, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial. The Lancet Diabetes and Endocrinology. 2019; 7(7):P515-527.
11. Husain M, Birkenfeld A, Donsmark A, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. New England Journal of Medicine. 2019; 381 (9):841-851.
12. Helfand C. Novo prices oral Rybelsus on par with injectable rivals, ending discount fears. FiercePharma. September 23, 2019.

PharmaNote®

Published by the UF Family Practice Residency Program and the Departments of Community Health & Family Medicine and Pharmacotherapy & Translational Research

University *of* Florida

Editor-in-Chief
John G. Gums, PharmD, FCCP

Managing Editor
Jason Powell, PharmD, BCACP

Associate Editor
R. Whit Curry, MD

Assistant Editor
Christopher R. Piszczatoski, PharmD